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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/071,541	05/04/1998	H.-J. SU HUANG	040750-5001	5607

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EXAMINER	
FONDA, KATHLEEN KAHLER	
ART UNIT	PAPER NUMBER
1623	19

DATE MAILED: 12/14/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/071,541	HUANG ET AL.	
	Examiner	Art Unit	
	Kathleen Kahler Fonda, Ph.D.	1623	

-- The MAILING DATE of this communication appears n the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 December 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *18* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-7 are again rejected, as set forth in the Office action of 06-06-01, under 35 U.S.C. 102(a) as being anticipated by NAGANE *et al.* (C24).

Applicant's arguments filed 12-06-01 have been fully considered but they are not persuasive. Applicant argues that NAGANE does not qualify as prior art under 102(a) because NAGANE was authored by a subset of the inventors named in the instant application. This argument is not convincing, because any difference between inventive entity and authorship is sufficient for application of 102(a); see MPEP 2132(III), citing *In re Katz*, 215 USPQ 14 (CCPA 1982).

Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over HAN *et al.* (K) in view of REED (A), further in view of TSAI *et al.* (aa).

Applicant claims a method of modulating inhibition of apoptosis in a target cell or tissue of a mutant EGFR gene by administering an effective amount of a tyrosine kinase inhibitor to the cell or tissue, in combination with a therapy which is effective to induce apoptosis or increase the rate of apoptosis.

The mutant EGFR gene may be ΔEGFR. The cell or tissue may be a tumor selected from the group consisting of glioma, breast cancer, lung cancer, and ovarian cancer. The therapy effective to induce apoptosis or increase the rate of apoptosis may be administration of cisplatin, paclitaxel, or vincristine. The tyrosine kinase inhibitor may be tyrphostin AG1478.

Applicant also claims a pharmaceutical composition and a kit for treating cancer comprising (A) an amount of an agent which is effective to induce apoptosis or increase the rate of apoptosis in a target cell or tissue, and (B) an amount of a tyrosine kinase inhibitor effective to reduce resistance mediated by a mutant EGFR to induction of apoptosis or to increased rate of apoptosis in a target cell or tissue. The agent may be cisplatin, paclitaxel, or vincristine. The tyrosine kinase inhibitor may be tyrphostin AG1478.

HAN teaches that tyrphostin AG1478 is a tyrosine kinase inhibitor that preferentially inhibits human glioma cells expressing the mutant ΔEGFR rather than wild-type EGFR; see the abstract. Additionally, HAN suggests that because tyrphostin AG1478 is a relatively specific inhibitor of ΔEGFR, it may be therapeutically useful with regard to glioblastomas, and breast, lung, and ovarian cancers, because the ΔEGFR mutation occurs

frequently in these cancers; see the abstract and the last two paragraphs on page 3861. HAN does not state that a tyrosine kinase inhibitor such as tyrphostin AG1478 should be administered together with a therapy which is effective to induce apoptosis or increase the rate of apoptosis.

REED teaches that cisplatin, taxol (also known as paclitaxel), and vincristine are known cancer chemotherapeutic agents which have in common an ability to induce apoptosis in cancer cells; see column 22, lines 4-15.

TSAI teaches that tyrphostin AG825 is a selective tyrosine kinase inhibitor able to enhance the sensitivity of certain cancer cells to chemotherapeutic agents doxorubicin, etoposide, and cis-diamminedichloroplatinum(II) (cisplatin). See, for example, the abstract.

It would have been obvious for a person of ordinary skill in the art at the time of the invention to provide a method of modulating inhibition of apoptosis in a target cell or tissue of a mutant EGFR gene by administering an effective amount of a tyrosine kinase inhibitor to the cell or tissue, in combination with a therapy which is effective to induce apoptosis or increase the rate of apoptosis, wherein the mutant EGFR gene is ΔEGFR; the cell or tissue is a tumor selected from the group consisting of glioma, breast cancer, lung cancer, and ovarian

cancer; the therapy effective to induce apoptosis or increase the rate of apoptosis is administration of cisplatin, paclitaxel, or vincristine; and the tyrosine kinase inhibitor is tyrphostin AG1478. An ordinarily skilled worker would have been motivated to do so in order to obtain the expected combination of therapeutic benefits with regard to cancer treatment. HAN had clearly suggested that use of tyrphostin AG1478, a selective tyrosine kinase inhibitor, for treatment of glioblastomas, and breast, lung, and ovarian cancers. As taught by REED, cisplatin, taxol (also known as paclitaxel), and vincristine were known cancer chemotherapeutic agents which could induce apoptosis in cancer cells. Because tyrphostin AG1478 had been taught by HAN to be a selective tyrosine kinase inhibitor, and because tyrphostin AG825 had been taught by TSAI to be a selective tyrosine kinase inhibitor, an ordinarily skilled worker would have expected the claimed combination therapy to result in modulation of the apoptosis-inhibiting effect of ΔEGFR, in accordance with the instant method claims.

It would furthermore have been obvious to provide a pharmaceutical composition or kit for treating cancer comprising (A) an amount of an agent which is effective to induce apoptosis or increase the rate of apoptosis in a target cell or tissue, and (B) an amount of a tyrosine kinase inhibitor effective to

reduce resistance mediated by a mutant EGFR to induction of apoptosis or to increased rate of apoptosis in a target cell or tissue, wherein the agent is cisplatin, paclitaxel, or vincristine; and the tyrosine kinase inhibitor is tyrphostin AG1478. An ordinarily skilled worker would have been motivated to do so in order to provide a therapeutically useful composition or kit to be used in cancer treatment (see the Examiner's explanation of obviousness of the method in the previous paragraph), which would enhance compliance with an appropriate treatment regimen, as well as provide added convenience for both clinician and patient.

Applicant's arguments filed 12-06-01 have been fully considered but they are not persuasive. The arguments to not apply specifically to the instant new ground of rejection, but they will be addressed to the extent that they might apply. Applicant argues that the references do not teach all claim limitations, and specifically that the amount of the claims is not taught or suggested. This is not persuasive because the amounts taught or suggested by the references are those which would meet the claim limitations. Furthermore, the underlying mechanism of Applicant's invention was appreciated by TSAI, so there would have been motivation to choose amounts as claimed. Applicant also argues that unexpected results have been

demonstrated. The Examiner does not agree. Granted, the results are not additive. However, this does not lead to the conclusion that they are unexpected. TSAI makes it clear that what would have been expected was an enhancement of the susceptibility of the cells to the apoptosis-enhancing or -inducing therapy (that is, for example, cisplatin). Just such an enhancement is demonstrated in Applicant's Figure 6B.

No claim is allowed.

Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on 12-06-01 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 609(B)(2)(i). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Papers relating to this application may be submitted to Technology Center 1600 by facsimile transmission. The number of the fax machine for official papers in Technology Center 1600 is (703) 308-4556. Any document submitted by facsimile transmission will be considered an official communication unless the cover sheet clearly indicates that it is an informal communication.

INTERNET INFORMATION: Secure and confidential access to patent application status information is now available; see http://www.uspto.gov/ebc/index.html for more information. Also, http://www.uspto.gov/web/offices/ac/comp/fin/clonedefault.htm may be used to pay patent maintenance fees, pay non-filing application fees, and maintain USPTO deposit accounts.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Kathleen Kahler Fonda, at telephone number (703) 308-1620. Examiner Fonda can generally be reached Tuesday through Friday, and on alternating Mondays, from 7:30 a.m. until 5:00 p.m. If the Examiner cannot be reached, questions may be addressed to

Supervisory Patent Examiner Gary Geist at (703) 308-1701. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-1235.

Kathleen Kahler Fonda, Ph.D.
Primary Examiner
Art Unit 1623